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- (71) Applicant (for all designated States except US): CELTECH R & D LIMITED [GB/GB]; 208 Bath Road, Slough, Berkshire SL1 3WE (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): HUMPHREYS, David, Paul [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). HEYWOOD, Sam, Phillip [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). CARRINGTON, Bruce [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB).
- (74) Agent: THOMPSON, John; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB).

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(54) Title: MODIFIED ANTIBODY FRAGMENTS

(57) Abstract: The present invention provides an antibody Fab or Fab' fragment to which at least one effector molecule is attached characterized in that the heavy chain in the fragment is not covalently bonded to the light chain and both the interchain cysteine of C<sub>1</sub> and the interchain cysteine of C<sub>H1</sub> have been replaced with another amino acid.

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- (51) International Patent Classification<sup>7</sup>: A61K 47/48 (74) Agent: THOMPSON, John; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB).
- (21) International Application Number: PCT/GB2004/002870 (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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- (71) Applicant (for all designated States except US): CELLTECH R & D LIMITED [GB/GB]; 208 Bath Road, Slough, Berkshire SL1 3WE (GB).
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- (75) Inventors/Applicants (for US only): HUMPHREYS, David, Paul [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). HEYWOOD, Sam, Philip [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). CARRINGTON, Bruce [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB).

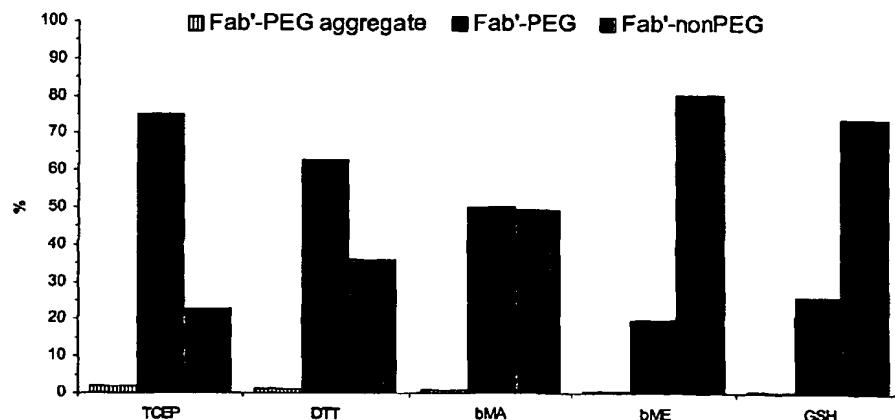
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(57) Abstract: The present invention provides an antibody Fab or Fab' fragment to which at least one effector molecule is attached characterized in that the heavy chain in the fragment is not covalently bonded to the light chain and both the interchain cysteine of C<sub>L</sub> and the interchain cysteine of C<sub>H1</sub> have been replaced with another amino acid.



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# INTERNATIONAL SEARCH REPORT

PCT/GB2004/002870

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, EMBASE, MEDLINE, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/15549 A (CELLTECH THERAPEUTICS LTD ; HUMPHREYS DAVID PAUL (GB)) 1 April 1999 (1999-04-01)	1-19, 27-30
Y	page 24, line 8 - line 24; claims; examples; table 1	1-30
X	WO 97/36932 A (KALLAND TERJE ; PHARMACIA & UPJOHN AB (SE); ANTONSSON PER (SE); HANSSO) 9 October 1997 (1997-10-09)	1-7,27, 28,30
Y	page 24, line 18 - page 25, line 6; claims; examples	1-30
P,X	EP 1 419 786 A (BRACCO IMAGING SPA) 19 May 2004 (2004-05-19)	1,6-9,30
P,Y	page 4, line 33 - page 7, line 24; claims; examples	1-30
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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- \*&\* document member of the same patent family

Date of the actual completion of the International search

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax. (+31-70) 340-3016

Authorized officer

Sommer, B

## INTERNATIONAL SEARCH REPORT

PCT/GB2004/002870

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HUMPHREYS D P ET AL: "Formation of dimeric Fab's in <i>Escherichia coli</i> : effect of hinge size and isotype, presence of interchain disulphide bond, Fab' expression levels, tail piece sequences and growth conditions" JOURNAL OF IMMUNOLOGICAL METHODS, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, NL, vol. 209, no. 2, 1997, pages 193-202, XP004103797 ISSN: 0022-1759 abstract; materials and methods; results; discussion; -----	1-15, 17, 18, 27, 28, 30
Y	HUMPHREYS D P ET AL: "Efficient site specific removal of a C-terminal FLAG fusion from a Fab' using copper(II) ion catalysed protein cleavage" PROTEIN ENGINEERING, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 12, no. 2, February 1999 (1999-02), pages 179-184, XP000882102 ISSN: 0269-2139 abstract; materials and methods; results; -----	1-11, 13, 15, 17, 27, 28, 30
Y	BURMEISTER GETZ E ET AL: "Comparison between the sulphhydryl reductants tris(2-carboxyethyl)phosphine and dithiothreitol for use in protein biochemistry" ANALYTICAL BIOCHEMISTRY, ACADEMIC PRESS, SAN DIEGO, CA, US, vol. 273, 15 August 1999 (1999-08-15), pages 73-80, XP000946001 ISSN: 0003-2697 abstract; discussion; -----	19-26

**INTERNATIONAL SEARCH REPORT**

PCT/GB2004/002870

**Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the International application and necessary to the claimed invention, the International search was carried out on the basis of:
  - a. type of material
    - a sequence listing
    - table(s) related to the sequence listing
  - b. format of material
    - in written format
    - in computer readable form
  - c. time of filing/furnishing
    - contained in the International application as filed
    - filed together with the International application in computer readable form
    - furnished subsequently to this Authority for the purpose of search
2.  In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

**INTERNATIONAL SEARCH REPORT**

PCT/GB2004/002870

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